Chapter 8.

Summary
Sleep has a fundamental and complex role in our daytime functioning. One of the many roles of sleep is to contribute to the conversion of novel emotional experiences into episodic memories that no longer evoke an emotional response. This process can be described as a “translation” of the brain activity during the initial emotional experience into a long-term memory trace. Previous research has shown that memory traces undergo large-scale reorganization over time. The encoding and retrieval of emotional events is initially dependent on the limbic circuit, later followed by consolidation and integration of the memory traces into the neocortex. Consolidation and integration requires potentiation of synaptic connections, while emotional adaptation may also depend on pruning and depotentiation of synaptic connections. This reorganization is facilitated by sleep. Not excluding a role for NREM sleep, the reorganization of emotional memory traces may critically depend on the unique neurophysiological and neurobiological characteristics of REM sleep, which allow for both potentiation and depotentiation of synaptic connections.

Stable REM sleep therefore seems important for the processing of emotional experiences and memories. Insomnia disorder (ID) is however characterised by restless REM sleep. We here use the term “restless REM sleep” to refer to REM sleep with a high number of phasic events including cortical arousals. These arousals may signify inappropriate continued activity of noradrenergic neurons in the locus coeruleus. This brainstem nucleus is normally strongly inhibited during REM sleep. The locus coeruleus has connections to many brain areas and provides those with noradrenalin, a potent neuromodulator that promotes synaptic potentiation. Inactivity of the locus coeruleus during normal REM sleep leads to a much lower noradrenalin level than during any other sleep-wake stage. As a result, REM sleep offers a unique time window for effective weakening of synaptic connections. However, continued activity of the locus coeruleus during restless REM sleep could disturb the precise balance in synaptic potentiation and depotentiation. The disturbed balance is likely to have a negative impact on overnight emotion regulation and memory processing of emotional experiences. We predict that chronically restless REM sleep and the consequent insufficient overnight emotion regulation may underlie the “hyperarousal” that is so characteristic of ID. The studies in this thesis investigate the hypotheses that
restless REM sleep in people with insomnia contributes to insufficient overnight emotion regulation and memory processing of emotional experiences, and that the resulting accumulation of emotional stress contributes to hyperarousal.

In chapter 1, we present the dual functionality of brain circuits involved in emotion processing. On the one hand, these circuits are involved in the formation of long-term memories. On the other hand, memory traces of emotional experiences are reorganized in such a way that they uncouple the corresponding original emotional response, thus effectively regulating emotional distress. Inadequate reorganization due to restless REM sleep could have severe repercussions, not only in ID, but also in other disorders with restless REM sleep such as depression and post-traumatic stress disorder (PTSD).

In chapter 2, we proposed that the association between restless REM sleep and hyperarousal—two key characteristics of ID—is mediated by insufficient overnight resolving of emotional distress. 1,199 participants of the Netherlands Sleep Registry completed questionnaires on insomnia severity, hyperarousal, self-conscious emotional distress, and thought-like nocturnal mentation. The latter was validated to be a proxy measure for restless REM sleep. An innovative aspect of the study was that it addressed the self-conscious emotion of shame, rather than commonly studied basic emotions. Self-conscious emotions, such as guilt, embarrassment, humiliation, pride and especially shame, are highly relevant in clinical psychiatry and psychology. For example, in sexually abused youth, shame contributes to risk of depression and the maintenance of PTSD symptoms, including hyperarousal. The associations between hyperarousal, emotional distress, and the restless REM sleep proxy measure were evaluated using structural equation modelling. The findings suggest that people with restless REM sleep more frequently report distress to last overnight, for one or many days. This long-lasting distress contributes to their chronic hyperarousal.

In chapter 3, we applied a within-subject repeated measures protocol to experimentally investigate the role of ID in the overnight adaptation to emotional experiences. We induced shame by exposing people with ID and normal sleepers to recordings of their own imperfect singing, four times across three consecutive days, in the morning and in the evening. After each exposure, the Experiential Shame Scale evaluated subjective emotional, physical, and social components of shame.
induced by the manipulation. In normal sleepers, the emotional and physical components of perceived shame had decreased during re-exposure if the previous exposure had immediately been followed by sleep. People with insomnia, on the other hand, experienced an adverse effect of sleep: immediate sleep in fact boosted the physical component of perceived shame distress during re-exposure. Rather than a mere loss of benefit, our findings uncovered that the restless sleep of people suffering from insomnia may actually be maladaptive and inverse the sleep-dependent adaptive processes, worsening next-days outcomes.

In chapter 4, we focussed on the activity of the limbic circuit during new and old emotional experiences. The sleep that follows new emotional experiences normally facilitates the translation of this limbic activity into long-term memory traces. These long-term memory traces are ultimately functionally dissociated from the limbic circuit. The findings in chapter 3 may suggest that people with insomnia have a chronic insufficiency to dissociate the limbic circuit. We used functional Magnetic Resonance Imaging (fMRI), a technique to measure brain activity, to assess which brain areas respond to new self-conscious emotional experiences and which brain areas respond to reliving self-conscious emotional experiences from the distant past. We then investigated the degree of overlap in brain areas involved in novel and past emotional experiences. Our hypothesis was that there would be no overlap in people with good sleep: the limbic circuit that activates with new emotional experiences should be dissociated from the memory traces that activate while reliving emotional experiences from the distant past. In people with insomnia, on the other hand, we expected overlap due to an incomplete dissociation of the limbic circuit. The results indicated that both groups showed a clear limbic response, specifically in the anterior cingulate cortex (ACC) during novel emotional experiences. In normal sleepers, reliving emotional distress from the distant past did not elicit a response in the ACC. In ID however, reliving emotional distress from the distant past elicited a response in the ACC that closely resembled its activation during novel distress. The findings are compatible with the idea of a chronic deficiency to dissociate the limbic circuit from long-term memory traces in ID. The deficiency seems to mainly affect the ACC in fMRI measurements.

In chapter 5, we evaluate the role of REM and non-REM sleep in the regulation of emotional distress. An animal model suggested that in particular REM sleep and
the preceding “transition to REM” (TTR) sleep are important for processing emotional experiences. We evaluated whether individual differences in the duration and fragmentation of the TTR and REM sleep periods were associated with overnight adaptation of the limbic response to a novel emotional stimulus. We also used classical conditioning to couple the emotional stimuli to odors. During sleep, we re-exposed participants to these odors to induce targeted memory reactivations. This allowed us to compare the effects of stable versus fragmented sleep periods on overnight limbic circuit adaptation. Repeated fMRI measurements before and after sleep showed that the overnight decrease in amygdala reactivity was proportional to the total duration of REM periods. While TTR sleep by itself did not influence overnight adaptation of amygdala reactivity, this sleep period did enhance the favourable effect of REM sleep periods. However, the positive association held only for restful REM sleep. The more interruptions a participant experienced during REM periods, the less limbic reactivity decreased overnight. Moreover, targeted memory reactivations during REM periods contributed to their favourable effect on the overnight decrease in limbic reactivity, but also enhanced the unfavourable effect of REM episode interruptions. The findings provide the most direct support for the hypothesis that ID involves an insufficiency to resolve emotional distress due to underlying maladaptive processes that manifest as restless REM sleep.

In chapter 6, we discuss that the identification of sleep states and their interruptions is exceptionally labour intensive. To facilitate future research on the study of electrophysiological anomalies in sleep of ID, we applied an automatic analysis approach on polysomnographic recordings in ID and normal sleepers. We found that light sleep was more dominant in ID and that participants with ID had more light sleep characteristics even during their deepest sleep. In addition, people with ID were more likely to transition from a deep sleep state to a light sleep state. These findings show that sleep in ID is not only characterized by increased REM sleep fragmentation as reported in chapter 4 and 5: also NREM sleep is less stable. The findings suggest that people with ID are hyperaroused even in their deepest sleep.

Chapter 7 discusses the possible mechanisms that underlie restless REM sleep. Altogether, the findings in this thesis suggest that people with ID experience a
maladaptive type of sleep, characterized by restless REM sleep, that results in long-lasting emotional distress by hampering overnight processing of emotional experiences. The accumulated distress may be what we refer to as hyperarousal, a key characteristic of ID. The findings of the current thesis are evaluated within the framework of a dual functionality of brain circuits involved in emotion processing. As mentioned above, these limbic circuits are, on the one hand, involved in the formation and re-consolidation of long-term memories, and on the other hand, also functionally dissociated from the long-term neuronal memory traces. The novel insights presented in this thesis could aid future efforts on the development of novel therapeutic interventions for ID, but also for disorders characterized by disturbed sleep and emotional distress, especially depression and anxiety disorders. The findings have commenced to reveal the underlying neurobiological processes and sleep conditions that reflect insufficient overnight emotional memory processing in insomnia.